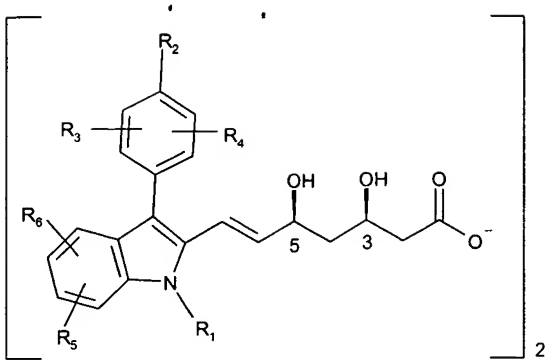

(IA)

wherein R_1 is alkyl, cycloalkyl or aralkyl; R_2, R_3 and R_4 are independently hydrogen, halogen or alkyl; R_5 and R_6 are independently hydrogen, halogen, alkyl, cycloalkyl, aralkyl, alkoxy or aralkoxy; and the hydroxyl group at the 3-position is in the R-configuration and at the 5-position in the S-configuration; or an enantiomer thereof; or a hydrate thereof; as obtainable by the methods of the present invention. More specifically, the invention provides a calcium salt of formula IA wherein R_1 is isopropyl, R_2 is fluorine and R_3, R_4, R_5 and R_6 are hydrogen, designated herein as Fluvastatin calcium, in a highly crystalline form. Furthermore, the present invention is directed to methods for the preparation of the crystalline Fluvastatin calcium, and to pharmaceutical compositions comprising the crystalline form.

Kathawala '772 discloses indole analogs of mevalonolactone and derivatives thereof. The Examiner notes that the Kathawala '772 discloses the potassium and sodium salts of the compounds, especially fluvastatin. In Table III of Kathawala "772 only discloses the potassium salt and sodium salt.

The Examiner notes that Kathawala '772 fails to disclose the calcium salt, but provides Ekwuribe '692 to disclose the obviousness between pharmaceutically acceptable salts. Ekwuribe '692 discloses synthesizing acylanilides and in column 11, lines 15-31 disclose a generic definition of pharmaceutically acceptable salts:

> Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, lactic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

The list provided by Ekwuribe '692 is a generic definition of possible pharmaceutically acceptable salts but the list provides no actual direction or suggestion that a particular salt would work with different compounds. Clearly, sodium salts are grouped with potassium salts as being alkali metal salts. However, calcium salts are grouped in alkaline earth metal salts.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that the combined references fail to disclose or suggest the calcium salts claimed in the present invention. The cited references fail to show an actual equivalence between sodium salts and calcium salts. More importantly, the Ekwuribe '692 reference is mainly an invitation to experiment, which is not the legal standard of obviousness. Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Applicants respectfully submit that the present invention provides a superior crystalline form of fluvastatin and its derivatives as claimed. The discovery that the calcium salt has greatly improved the crystallinity, which then leads to chemical stability and longer shelf life, is clearly a non-obvious step. The proposed *prima facie* case of obviousness is merely an "obvious to try" without the proper motivation to make the calcium salt as required by the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Conclusion

Applicants have addressed all outstanding issues present in the Office Action. Applicants respectfully submit the present invention is patentable as claimed. The commissioner is hereby authorized to charge any additional fees that may be due, or to credit any overpayment, to Account number 19-0134.

Respectfully submitted,

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